

REMARKS

In this Amendment, Claims 1, 5, 9, 29, 33, 37 and 50 are amended, and Claims 10 and 14-28 are cancelled. Applicants reserve the right to file a continuation or divisional application on any subject matter cancelled by way of this amendment. Claims 1-9, and 29-50 are pending in this application. (It was incorrectly stated in the Office Action of August 14, 2002 that Claim 10 was cancelled.) Claims 42 and 46 are allowed. The amendments to the claims do not add new subject matter.

Entry of this Amendment and Reply is proper under 37 C.F.R. § 1.116, because (1) the Amendment does not raise any new issue requiring further search and/or consideration, as the claim amendments address issues previously discussed throughout prosecution; and (2) will reduce the number of issues for appeal. The Amendment is necessary and was not earlier presented, because it is made in response to arguments raised in the final rejection and in further telephonic discussions with the Examiner. Entry of the Amendment, reexamination and further and favorable consideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are thus respectfully requested.

Applicants note that a Notice of Appeal was filed on November 12, 2002.

Applicants acknowledge the Examiner's withdrawal of the rejections of Claims 11-13 under 35 U.S.C. § 112, first paragraph and Claims 10, 37-38 under 35 U.S.C. § 112, second paragraph. See August 14, 2002 Office Action, pages 2-3.

Amendments to the Claims

Support for amendments to Claims 1, 5, 9, 29, 33, 37, and 50 can be found in the Specification, for example, at page 21, line 5-17. These claims have been amended to delete duplicative recitation of meaning as one skilled in the art would understand the definition of the composition by the term "isolated" alone.

The term "isolated" is clearly defined in the Specification and its meaning is well understood in the art. For many years, skilled artisans have referred to "isolated sequences" or "molecules" as those compounds isolated from their naturally-occurring

cellular or compositional states. In particular, isolated nucleic acid or polypeptide sequences are defined in the art as those whose bases or amino acid structures are known. The United States Patent and Trademark Office itself regularly issues patents with claims to isolated nucleic acid or polypeptide sequences. See, for example, U.S. Patent No. 6,380,370. All those of skill in the art are given notice by these claims that the composition claimed is of a particular nucleotide or amino acid sequence.

Furthermore, the Examiner's original 102 rejection in the second Office Action, dated February 22, 2001 (Paper No. 19), based on Haertl et al. states that "bacteria only have a single chromosome and upon isolation of the chromosomal DNA from the cell, the isolated nucleic acid would comprise the coding regions for the polypeptides produced by *E. cloacae*." Applicants assert that the argument has no merit because no sequences were disclosed by Haertl et al. and as thus cannot anticipate the claimed nucleic acid sequence. Also, "isolated" is a well known term in the art. As a result, Applicants have amended the claims to recite the original claim language.

Rejection of Claims 1-10, 29-41, 43-45, and 47-50 Under 35 U.S.C. § 101

Claims 1-10, 29-41, 43-45, and 47-50 are rejected under 35 U.S.C. §101 because the claimed invention is not supported by a specific, credible, and substantial utility or a well-established utility for the elected invention.

Applicants assert that a well-established utility and a specific, substantial, and credible utility have been established for the claimed invention. At a minimum, the elected sequences and the compositions of the present invention may be used as molecular targets for identification of new antimicrobials agents, probes for diagnostic assays, and targets for vaccine development. See Exhibits 1, 2, and 3.

The Manual of Patent Examining Procedure (MPEP) states at § 2107.01, that research tools can be “useful” in a patent sense:

Many research tools such as . . . nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact “useful” in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

Therefore, nucleotide sequencing techniques, which can include microbial genomic databases containing nucleic acid sequences, amino acid sequences and sequence homology information of bacterial genes that are, in turn, useful in the functional analysis of the bacterial genome, can meet the utility requirement of 35 U.S.C. § 101 if, for example, the nucleic acid sequences and proteins encoded by the nucleic acid sequences have a well-established utility or, in the alternative, a specific, substantial, and credible utility such as in the development of antibiotics, diagnostics, vaccines, and drugs to treat humans afflicted with infection caused by the bacteria.

I. The Specification Asserts A Well-Established Utility For The Claimed Invention

The MPEP states, at § 2107.02B, that the utility of 35 U.S.C. § 101 is met, even if a specific, substantial, and credible utility for the claimed invention is not asserted in the Specification, if such utility is well-established:

An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

The guidelines for examination of patent applications under 35 U.S.C. § 101, “utility” requirement referenced by the Examiner, as shown in the Federal Register, Vol. 66, No. 4, pages 1092-1099, at page 1095, states:

By statute, a patent is required to disclose one practical utility. If a well-established utility is readily apparent, the disclosure is deemed to be implicit.

The Federal Register, Vol. 66, No. 4, page 1097 also states:

Only one specific, substantial and credible utility is required to satisfy the statutory requirement. Where one or more well-established utilities would have been readily apparent to those of skill in the art at the time of the invention, an [A]pplicant may rely on any one of those utilities without prejudice. (emphasis added).

The invention involves nucleic acid and amino acid sequences relating to *Enterobacter cloacae*. Many sources written by those skilled in the biological sciences describe the utility of sequence information from microbial pathogens as well-established in the art. For example, as shown in Exhibit 1, Moir, D.T., *et al.*, *Antimicrob. Agents Chemother.* 43: 439-446 (1999), states, on page 439, that genomic sequence information has provided a wealth of information useful to assist in the development of strategies for antimicrobial drug discovery:

[H]igh-throughput automated random genomic DNA sequencing together with robust fragment assembly tools has delivered a wealth of genomic sequence information to assist in the search for new targets. In many cases, entire biochemical pathways can be reconstructed and compared in different pathogens.

Further, Moir *et al.*, states, on page 440-441, that essential genomic sequence information is useful in identifying potential targets for new antimicrobials:

Genes which are essential to pathogenesis and prevent colony formation in a conditional-lethal manner are potential targets for new antimicrobials.

In addition, Tatusov, R.L., *et al.*, *Science* 278: 631-637 (1997), Exhibit 2, on page 631, states that comparisons of complete genomic sequences of bacteria are useful and can be critically important to the development of targets for new antibiotics:

With multiple genome sequences, it is possible to delineate protein families that are highly conserved in one domain of life but are missing in the others. Such information may be critically

important: For example, the families that are conserved among bacteria but are missing in eukaryotes comprise the pool of potential targets for broad-spectrum antibiotics.

Smith, D.R., *TIBTECH* 14: 290-293(1996), Exhibit 3, states, on pages 291-292, that the first task in identifying new strategies for therapeutics and vaccine targets is to identify genes of the microbial organism and that the second task is identifying sequence homology which is useful in the analysis of gene products. Specifically, Smith states on page 292:

The second phase in the analysis of bacterial genomes is to identify the function of as many genes as possible. Currently, sequence homology is the most powerful tool. A high degree of homology between the putative translation product of a newly identified gene and an enzyme whose function has been thoroughly studied in other organisms, provides strong support for the function of that protein.

In addition, Smith states, on page 293, that microbial genome sequence information is useful in new strategies for identifying drug or vaccine development targets by targeting essential genes:

The techniques described in the previous section can be used to identify genes in specific functional categories that may represent good targets for drug or vaccine development. In general, when developing new antibiotics, one is interested in genes that are essential under all growth conditions . . . .

Furthermore, the Specification discusses additional well-established utilities of the *E. cloacae* nucleotide sequences. For example, the nucleotide sequences can be useful for developing probes used in diagnostics to detect the presence of the *E. cloacae* pathogen. See Specification, page 34, line 15 to page 35, line 6. The nucleotide sequences can be useful for creating primers to amplify *E. cloacae* nucleic acids sequences. See Specification, page 35, line 23 to page 36, line 17. The nucleotide sequences are useful for the creation of antisense agents, which can be used to prevent the expression of *E. cloacae* genes. See Specification, page 36, line 19 to page 37, line 12.

The usefulness of the claimed invention includes providing information to assist in new drug discoveries, assisting in the development of targets for new antibiotics, and

identifying new drug or vaccine development targets. The claimed invention can also be used as a means of diagnosing a patient or a biological sample with *E. cloacae*. These uses are apparent and implied by the Specification when taken with knowledge of one skilled in the art at the time of Applicants' invention. The claimed invention has a well-established utility. Thus, Applicants respectfully request the withdrawal of the 35 U.S.C. §101 rejection.

II. The Specification Asserts A Credible, Specific, And Substantial Utility For The Claimed Invention

A. The claimed sequences have a specific utility.

The MPEP states at § 2107.01 that a specific utility is:

A "specific utility" is specific to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of invention. . . . [T]he situation where an [A]pplicant discloses a specific biological activity and reasonably correlates that activity to a disease condition. Assertions falling within the . . . category are sufficient to identify a specific utility for the invention.

Applicants direct the Examiner's attention to the a summary of Table 2 of the Specification as filed. The summary contains the nucleotide SEQ ID in the first column along with the corresponding protein in the second column. For example, the nucleotide sequence in SEQ ID NO:1394 encodes the amino acid sequence in SEQ ID NO:7056.

Moreover, Applicants provide results herein below from sequence alignments for the amino acid sequences encoded by the nucleotide sequences of the presently claimed invention. These alignments refer to the reference sequences provided in Table 2 of the Specification. The summary table provides the claimed nucleotide SEQ ID NO. and the corresponding amino acid SEQ ID NO. as well as the percent identity. In addition to the summary table below, the sequence alignment itself is submitted as Exhibit 4 to visually reinforce that the claimed sequences are homologs of the reference sequences. Identical residues in the alignments are connected by lines, and similar (as opposed to identical)

amino acids are identified by dots between the similar residues. These results were produced using the GCG Best Fit algorithm, which makes an optimal alignment between segments of sequences based on similarity.

Summary Table of Sequence Alignments and  
Table 2 of Specification

Claimed Nucleotide SEQ ID NO:	Corresponding Amino Acid SEQ ID NO:	Reference Sequence	Refer ence Gene Name	% identity
1394	7056	B1135	ymfc	85.0

These sequence alignments show that there is a high degree of identity and similarity between the claimed sequences and the reference sequences from Table 2 of the Specification. By way of explanation of sequence alignment accuracy, Applicants submit the reference (Exhibit 5) by Rost, PROTEIN ENGINEERING, 12:85-94 (1999). Rost discloses that the accuracy of the results of sequence alignments is much higher when the sequence identity percentage is greater than 35 %, because the number of false positives is drastically reduced at this point. Thus, to those of skill in the art, a sequence identity higher than 35 % is an accurate result. See Rost, pages 91-92.

Applicants note that the alignment of the claimed sequence yield a sequence identity percentage much higher than the threshold of 35 %. The sequence identity is 85 %. Applicants point to the paragraph at the bottom of the first column of page 92 of the Rost publication, wherein Rost states that "[f]rom 100-35 % sequence identity, any residue exchange resulting in a stable structure maintains structure."

The Examiner also states that:

[T]he primary structure of a putative polypeptide does not define the nucleic acid that encodes the polypeptide as a

specific diagnostic agent and the polypeptide is not defined to have any specific function, just a putative structure.

The Examiner has taken the position that the functional identification of polypeptide SEQ ID NO:7056 encoded by SEQ ID NO:1394 in Table 2 of the specification is identified at page 53, line 7 as "putative." The Examiner is reminded that the definition of putative is (1) commonly accepted or supposed, (2) assumed to exist or have existed (See, for example, Merriam-Webster Collegiate Dictionary Online <http://www.m-w.com/home.htm>). Therefore, unless presented with a reason to doubt the identification, it should be taken as commonly accepted. The applicable standard is a credible utility and not a proven or certain utility. See, Utility Examination Guidelines, 66 FR 1092 (Jan. 5, 2001). The training manuals describe how this standard is to be applied as follows:

Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. See the Revised Interim Utility Guidelines Training Materials of the U.S.P.T.O. at page 5.

The Examiner has not shown that either the logic underlying Applicant's assertion of utility is seriously flawed or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

The Examiner states that "[h]omology with other known polypeptides or nucleic acids does not define a nucleic acid as a specific diagnostic reagent, nor does it establish that polypeptide's specific function." Furthermore, the Examiner requests Applicant to point to the section of the instant specification that defines the claimed nucleic acid to encode a polypeptide with pseudouridine synthase biological activity. Applicants have. By providing these search results, the specific function of the claimed nucleic acid is

disclosed. To one of skill in the art, it encodes a polypeptide with pseudouridine synthase activity.

Nucleic acid sequences and their encoded amino acid sequences, which are homologous to known sequences with accepted utility, can meet the utility requirement of 35 U.S.C. § 101, if, for example, the homologous nucleic acid and amino acid sequences have accepted utility and the nucleic acid and amino acids sequences of the invention assert a specific, substantial and credible utility, such as the function of the homologous protein. As stated in the Federal Register at Vol. 66, No. 4, at page 1096:

More specifically, when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the [E]xaminer unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. "[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient." (citations omitted).

The claimed sequences of this invention meet this requirement as shown in the above table and discussed below.

SEQ ID NO:1394, which codes for SEQ ID NO:7056, encodes a homolog to *E. coli* pseudouridine synthase. Applicants would like to reference Koonin, submitted with Applicants' Amendment and Reply of June 22, 2001, Koonin, Nucleic Acids Res. 24(12):2411-5 (1996), which discloses that:

[I]t is shown that the four recently described pseudouridine syntheses with different specificities belong to four distinct families. Three of these families share two conserved motifs that are likely to be directly involved in catalysis. One of these motifs is detected also in two other families of enzymes that specifically bind uridine, namely deoxycytidine triphosphate deaminases and deoxyuridine triphosphatases. It is proposed that this motif is an essential part of the uridine-binding site. Two of the pseudouridine synthase, one of which modifies the anticodon arm of tRNAs and the other is predicted to modify a portion of the large ribosomal subunit RNA belonging to the peptidyltransferase center, are encoded in all extensively sequenced genomes, including the

'minimal' genome of *Mycoplasma genitalium*. These particular RNA modifications and the respective enzymes are likely to be essential for the functioning of any cell.

Pseudouridine synthase is essential to the functioning of the cell. The high homology of Applicant's claimed sequence to pseudouridine synthase is a result of the maintenance of the conserved motifs of pseudouridine synthases and points to its essentiality in the cell. The disclosed sequences and the identification of this function meet the Utility Guidelines of the Federal Register; therefore, the Examiner must accept the asserted utility.

The Examiner states that "Koonin et al does not mention anything about *E. cloacae* whatsoever in the reference. One of skill in the art would not have ascertained that the *E. cloacae* nucleic acid that encodes pseudouridine synthase biological activity was known in light of the disclosure provided by Koonin et al."

One of skill in the art at the priority date of the present application would envision that the pseudouridine synthases taught by Koonin *et al.* has the same function across bacterial species including *E. cloacae* because of the sequence identity and conserved signature motifs. ( Nucleic Acids Research, 24:2411-15, (1996)). Koonin teaches that pseudouridine synthases across bacterial genomes have certain signature motifs beyond the PROSITE motif. All three signature motifs taught by Koonin are found in the polypeptide SEQ ID NO:7056 encoded by SEQ ID NO.:1394 as shown on page 11 of Applicants' Amendment and Reply of June 22, 2001. The teachings of Koonin present motifs which complement and expand on the PROSITE entries. Koonin also teaches that pseudouridine synthases perform essential functions. Koonin teaches both the means of identification and the essential nature of the presently elected sequences of the invention.

The Examiner states that:

The specific accession number P75966 was created November 1, 1997, but the comment section appears to be dated November 23, 1998 and defines the hypothetical protein to be a member of the pseudouridine synthase family. The description was provided to the public about *ymfc* after the filing date of the instant specification.

Applicants note that the Examiner has mistakenly interpreted the comment of the NCBI entry to indicate that the functional identification is dated November 23, 1998. However, this comment only indicates that entry gi:2501525 was replaced with a newer entry gi:3916025 on that date. The Koonin reference submitted by Applicants is the prior entry apparently dating from November 1, 1997. An unidentified portion of the annotation may have been updated on July 15, 1998. However, both the creation of entry gi:2501525 and the unidentified update precedes the filing date of the present application. Furthermore, Applicants wish to point out that Reference Sequence B1135 listed in Table 2 was already in the public domain at the time of the filing of the application. By reference to public databases known to and routinely used by one of skill in the art, one would have appreciated that this information identifies the polypeptide product as pseudouridine synthase of the RsuA family. For example, SWISSPROT entry accession No. P75966 (NCBI entry PID gi:2501525 and gi:3916025) was created November 1, 1997 prior to the filing of the application.

Applicants' claimed invention provides nucleic acid sequences that encode polypeptides used in diagnostics and therapeutics. Specifically, Applicants' claimed invention includes a wide variety of nucleic acid sequences which encode proteins that share homology with known proteins that have utility, several of which have been shown to be essential to the life of cell. Thus, the claimed invention has a specific utility.

**B. The claimed sequences have a substantial utility.**

The MPEP states at § 2107.01 that a substantial utility is defined as a utility that "defines a 'real world' use." For example, "a therapeutic method of treating a known or newly discovered disease . . . that themselves have a 'substantial utility' define a 'real world' context of use." *Id.* Given the important applications described in Moir *et al.*, Tatusov *et al.*, and Smith, Applicants submit that the development of treatments for bacterial infections constitute a "real world" use. Therefore, the presently claimed invention provides a satisfactory substantial utility.

C. The claimed sequences have a credible utility.

Regarding credible utility, according to the MPEP at § 2107.01, "in view of the rare nature of such cases, Office personnel should not label an asserted utility 'incredible,' 'speculative' or otherwise unless it is clear that a rejection based on 'lack of utility' is proper." A credible utility is "assessed from the perspective of one of ordinary skill in the art, in view of the disclosure and any other evidence of record that is probative of the [A]pplicants assertions." Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001). The claimed sequences can be used as probes, capture ligands, primers, antisense agents, or diagnostic markers for the detection of specific disease causing pathogens. See Specification, page 34, line 15 to page 37, line 12. The relationship of the claimed nucleic acid sequences and corresponding amino acid sequences to essential genes of other pathogens with clearly, defined functions and usefulness demonstrate that an Examiner would have no reason to dismiss the asserted utility as incredible or speculative. Thus, the claimed invention has a credible utility.

D. Conclusion

Since the claimed invention has a well-established and a specific, substantial, and credible utility, the claimed invention meets the requirements of 35 U.S.C. § 101. Thus, Applicants respectfully request the withdrawal of the 35 U.S.C. §101 rejection.

Rejection of Claims 1-10, 29-41, 43-45, and 47-50 Under 35 U.S.C. § 112, first paragraph

Claims 1-10, 29-41, 43-45, and 47-50 are rejected under U.S.C. § 112, First Paragraph, since the claimed invention is not supported by either a specific, credible, and substantial utility or a well-established utility.

Applicants' argument *supra* demonstrates that the claimed invention is supported by a specific, credible, and substantial utility and a well-established utility. Accordingly, Applicants respectfully request the removal of the U.S.C. § 112, First Paragraph rejection.

Rejection of Claims 29, 33, and 37-38 Under 35 U.S.C. § 112, first paragraph

Claims 29, 33, and 37-38 stand rejected under 35 U.S.C. § 112, first paragraph.

The Examiner states that:

[T]he specification does not reasonably provide enablement for the use of any nucleic acid that only shares 70% sequence identity with SEQ ID NO:1394, based upon nucleic acid changes encompassed by claiming the isolated nucleic acid sequences by SEQ ID NO:7056.

Applicants respectfully traverse. As stated on page 1102 of the Federal Register, Vol. 66, No. 4, disclosure of a single species can provide an adequate written description of a generic claim, if one skilled in the art would recognize that the disclosure of the species includes the genus:

The Guidelines now indicate that a single species may, in some instances, provide an adequate written description of a generic claim when the description of the species would evidence to one of ordinary skill in the art that the invention includes the genus.

A disclosure "is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." *In re Grimme, Keil and Schmitz*, 124 U.S.P.Q. 449, 502 (C.C.P.A. 1960).

The Specification as filed provides ample support for the Claims.

For example, support for Claims 29, and 33 can be found on page 43 of the Specification, which states that:

[D]ue to the degeneracy of the genetic code, many different nucleotide sequences can encode polypeptides having the amino acid sequences defined by SEQ ID NO: 5663 - SEQ ID NO: 11324 or sub-sequences thereof. The codons can be selected for optimal expression in prokaryotic or eukaryotic systems. Such degenerate variants are also encompassed by this invention.

Support for Claims 37, and 38 can be found on page 10 of the Specification, which states that:

[T]he polypeptide has an amino acid sequence at least about 60%,

70%, 80%, 90%, 95%, 98%, or 99% identical to an amino acid sequence of the invention contained in the Sequence Listing[.]

Moreover, additional support for Claims 37, and 38 can be found on page 10 of the Specification, which states that:

[T]he *E. cloacae* polypeptide is encoded by a nucleic acid of the invention contained in the Sequence Listing, or by a nucleic acid having at least about 60%, 70%, 80%, 90%, 95%, 98%, or 99% homology with a nucleic acid of the invention contained in the Sequence Listing.

One of ordinary skill in the art would have envisioned the scope of the invention to comprise SEQ ID NO:1394 and additional nucleic acid sequences that encode for SEQ ID NO:7056 that are based on the degeneracy of the genetic code. One of ordinary skill in the art would easily have identified multiple nucleic acid codons capable of encoding a given amino acid residue and, as a result, envision combinations of these codons to comprise numerous other nucleotide sequences encoding SEQ ID NO:7056. Thus, there is ample support for the claims as provided for by the Specification.

The Examiner states that

[T]he specification does not teach what function the polypeptide has, or regions of the nucleic acid can be changed, or are conserved . . . . [A] nucleic acid claimed based upon the recited amino acid sequence would not be predictably detect *E. cloacae* specific . . . . No specific guidance has been provided in the instant specification and the person of skill in the art would not be able to make and use a nucleic acid to predictably detect *E. cloacae* which shares about 67% sequence identity with SEQ ID 1394, or a sequence of any size that shares 90 or 95% with SEQ ID NO:7056[.]

Prior to the filing of this patent application, functional domains for rsuA in other species were well known in the art. As shown supra, the specification discloses that the nucleotide sequence represented by SEQ ID NO: 1394 encodes a polypeptide with a sequence identity to the polypeptide coded for by the pseudouridine synthase gene (rsuA). See Table 2 and the Sequence Listing as filed. For example, the PROSITE

reference lists the functional domains for pseudouridine synthase. Because functional domains for the *rsuA* gene were well known in the art, one of ordinary skill in the art would have been able to envision and utilize isolated amino acids containing fragments with these functional domains having sequence identity to SEQ ID NO: 7056 at the time this application was filed. Moreover, these functional domains could be used in the screening of novel broad spectrum antibiotics across bacterial species.

Furthermore, Koonin teaches that pseudouridine synthases have certain signature motifs beyond the PROSITE motif. All three signature motifs taught by Koonin are found in the polypeptide SEQ ID NO:7056 encoded by SEQ ID NO.:1394 as shown on page 11 of Applicants' Amendment and Reply of June 22, 2001. The teachings of Koonin present motifs identified with details which complement and expand on the PROSITE entries. Koonin also teaches that pseudouridine synthases perform essential functions. Since knowledge of the signature motifs are well known in the art, a person of ordinary skill in the art would be able to detect *E. cloacae* specific nucleic acid sequences. Accordingly, Applicants respectfully submit that the invention as described in the Specification shows that the Applicants have possession of the claimed invention under 35 U.S.C. § 112 and respectfully request the withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 5, 9, 29, and 50 Under 35 U.S.C. § 102

Claims 5, 9, 29, and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Blattner et al. ("Blattner") or Oshima et al. ("Oshima"). The Examiner states, in Office Action dated August 14<sup>th</sup>, 2002, page 7, that:

[T]he sequence alignment of Blattner et al's sequence with the sequence of the instant Specification, with respect to a polynucleotide, SEQ ID NO: 1394, that encodes for the amino acid sequence of SEQ ID NO 7056, shows 94% over all sequence identity for the nucleic acid coding sequence.

Furthermore, the Examiner states:

The amino acid sequence of Blattner shows two extensive stretches of identical amino acids, the first being a sequence of 25

sequential or consecutive amino acids that would be encoded by 75 nucleotides that would hybridize to the instantly claimed nucleic acid, and the second being a sequence of 52 sequential or consecutive amino acids that would be encoded by 156 nucleotides that would hybridize to the instantly claimed nucleic acid . . . .

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *W.L. Gore & Associates v. Garlock, Inc.*, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); *Connell v. Sears Roebuck & Co.*, 220 USPQ 193, 198 (Fed. Cir. 1983); *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); *In re Spada*, 15 USPQ2d 1655 (Fed. Cir. 1990); MPEP § 2131.

"An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Fiers v. Revel*, 984 F.2d 1164, 1170. Under *Fiers*, possession of the complete nucleic acid sequence must be in the prior art to anticipate a claimed nucleic acid sequence. It is not sufficient to use an amino acid sequence to anticipate a nucleic acid sequence. It is incorrect and improper to apply fully degenerate probes from an amino acid sequence to screen a genomic DNA library. The Examiner must first have possession of a nucleic acid sequence before citing the nucleic acid sequence against the Applicants. As a result, the 25 or 52 consecutive amino acids cited in *Blattner* cannot anticipate 75 or 156 consecutive nucleic acids without possession of the DNA sequence itself.

Regarding claim 29, the Examiner cited a nucleotide sequence after reverse blasting SEQ ID NO:7056 against a nucleotide database. The reverse BLAST program returned a nucleic acid sequence that encoded an entirely-different protein from SEQ ID No:7056. The cited nucleic acid sequence was NOT an EXACT match to the claimed nucleic acid sequence. A reference cited under 35 U.S.C. Section 102 must anticipate each and every element of a claim. As a result, the Examiner cannot apply that nucleic acid sequence against Applicants' claimed nucleic acid sequences because the sequence

identity between the cited sequence and the claimed sequence is not 100% identical. Thus, the references cited by the Examiner cannot anticipate the invention of claim 29.

Regarding claims 5, 9, and 50, the Sequence Alignments, as shown in Exhibit 6, for the nucleic acid show no more than 23 consecutive nucleotides of SEQ ID NO.:1394. Neither Blattner nor Oshima teaches or suggests 25 or 30 consecutive nucleotides of SEQ ID NO.:1394. Thus, the references cannot anticipate the claimed invention of claims 5, 9, and 50.

Accordingly, Applicants respectfully submit that the invention as described in the specification shows that the Applicants' invention is distinguishable from that of Blattner or Oshima and respectfully request the withdrawal of the rejection under 35 U.S.C. § 102(b).

SUMMARY AND CONCLUSION

Applicants' claimed invention, as amended, meets the requirements of 35 U.S.C. §§ 101, 102, and 112, first paragraph.

Reconsideration and withdrawal of the pending rejections are respectfully requested. If the Examiner feels that a telephone conference would expedite prosecution of this application, the Examiner is invited to call the undersigned at (781) 398-2548.

Respectfully submitted,

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1. (Thrice Amended) An isolated nucleic acid encoding an *E. cloacae* polypeptide wherein the nucleic acid comprises SEQ ID NO: 1394[, and wherein SEQ ID NO: 1394 is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome].
5. (Thrice Amended) An isolated nucleic acid encoding an *E. cloacae* polypeptide or a fragment thereof, wherein the nucleic acid comprises at least 25 sequential bases of SEQ ID NO: 1394[, and wherein SEQ ID NO: 1394 is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome].
9. (Thrice Amended) A probe comprising a nucleotide sequence including at least 25 sequential nucleotides of SEQ ID NO: 1394[, and wherein SEQ ID NO: 1394 is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome].
29. (Amended) An isolated nucleic acid encoding a polypeptide which comprises SEQ ID NO: 7056[, wherein the isolated nucleic acid is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome].
33. (Amended) An isolated nucleic acid which encodes a polypeptide of *E. cloacae* consisting of a range of residues which is 3 - 222, 6-222, or 13 - 222 of SEQ ID NO: 7056[, wherein the isolated nucleic acid is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome].
37. (Amended) An isolated nucleic acid encoding a polypeptide which comprises at least 90% sequence identity with SEQ ID NO: 7056[, wherein the isolated nucleic

acid is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome].

50. (Amended) A probe comprising a nucleotide sequence including at least 30 sequential nucleotides of SEQ ID NO: 1394[, wherein the isolated nucleic acid is not immediately contiguous with both of the coding sequences with which SEQ ID NO: 1394 is immediately contiguous in the naturally-occurring *E. cloacae* genome].